# MELANOCORTIN AGENTS FOR USE IN THE THERAPEUTIC TREATMENT OF MELANOMA, TUMORS OF THE GASTROINTESTINAL TRACT, AND THYROID CARCINOMA

**[0001]** The present invention falls within the field of therapeutic treatments of tumor pathologies, particularly solid tumors, more particularly melanoma, tumors of the gastrointestinal tract, and thyroid carcinoma.

**[0002]** Despite the significant progress achieved in recent years by surgical therapy, which represents the preferred intervention for this type of tumors in the early stage, the incidence of mortality due to melanoma, gastrointestinal tumors and thyroid carcinoma remains high.

**[0003]** Melanoma is a cutaneous malignant neoplasm that originates from melanocytes, i.e. skin cells located at the level of the epidermis. The incidence of this neoplasm is constantly increasing, although its frequency is significantly lower than basal cell and spinocellular carcinomas. Melanoma can occur in any body district, on healthy skin or on a congenital or acquired melanocytic nevus. More rarely, it occurs in different sites, such as the eye (the conjunctiva or choroid), the vulva, the anus, the oral or nasal cavity. In a non-negligible percentage of cases the diagnosis is made following the appearance of lymph node or visceral metastases with no clinical evidence of the primitive melanoma ("unknown primitive melanoma"). In recent years, significant progress in the biomolecular field has led to the identification of specific mutations in the melanocyte cell. 50-60% of melanomas exhibit BRAF mutations, which is a gene coding for a protein kinase involved in cell growth regulation. NRAS mutation is found in 15-30% of melanomas and is mutually exclusive with BRAF mutation; p16 and p14ARF (CDKN2A) are often inactivated in melanomas that occur on chronically photoexposed skin, while cKIT mutations are found in acral/mucosal melanomas and on photodamaged skin.

**[0004]** According to the Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute, the incidence of melanoma in the US was estimated at 6.8 per 100,000 person-year in 1973, while in 2005 this incidence increased to 20.8. However, there are many variations in incidence in the different ethnic groups and geographical areas. The trend is constantly increasing in Italy too, with a tendency to a doubling of melanoma diagnoses in 10 years. In Northern Europe and the US, excluding skin cancers, this tumor accounts for 2-3% of all malignant tumors. In Europe the frequency of melanoma is 1% of all male tumors and 1.8% of all female tumors. The country with the highest incidence of melanoma in the world is Australia (55.8 cases per 100,000 inhabitants in men and 41.1 in women), followed by New Zealand and Northern Europe, whereas the incidence of the tumor is lower in Japan and Central Africa (0.4/100,000 inhabitants). In Italy, incidence rates range from 6 cases per 100,000 in the south to 15 cases per 100,000 in the northern regions. There are differences among the various regions: the highest rates, between 12.5 and 13, are recorded in Friuli Venezia Giulia, Romagna, Marche, Trentino and Tuscany (AIRTUM, Associazione Italiana Registri Tumori). The median age at diagnosis is approximately 50 years, earlier than that of other cutaneous epithelial neoplasms.

**[0005]** Among the solid tumors characterized by a marked aggressiveness are also gastrointestinal tumors, including colorectal carcinomas, pancreatic carcinoma, gastric carcinoma, esophagus cancer, and biliary tract cancer. The overall incidence of gastrointestinal malignancies appears to be increasing, and supporting these data, gastric cancer is reported in Europe as the fourth leading cause of death from cancer and the second in the world. Thyroid carcinoma also exhibits a significant trend in the increase in the number of cases, for example, being the fifth most frequent tumor in the United States.

**[0006]** The clinical relevance of the aforementioned tumor pathologies—melanoma, tumors of the gastrointestinal tract and thyroid carcinoma—is also increased both by the high metastatic potential they have, with appearance of metastases in 15-35% of patients, and the high capacity of locoregional infiltration. In addition, patients suffering from these advanced-stage tumors generally experience the onset of the "neoplastic cachexia" pathological condition, a complex metabolic syndrome characterized by weight loss and muscular atrophy.

**[0007]** Currently, the treatment of choice for these neoplasms diagnosed in the early stage remains surgery, and drug therapy is generally implemented after the intervention as an adjuvant therapy or in the presence of metastatic disease. The only drug for which a potential efficacy has so far been documented in the adjuvant treatment of melanoma is interferon-alpha (IFN). Studies published in the literature have used schedules with different doses of IFN, but the most effective doses and administration modes have not been uniquely defined yet. Cutaneous or subcutaneous involvement is a frequent event in the clinical course of melanoma: skin lesions are present in 10-17% of patients and in almost 50% of patients with metastatic disease. The choice of the treatment method for skin metastases depends on the location and number of lesions, the systemic involvement, the age and general condition of the patients. Surgery is the most appropriate treatment when the lesions are clustered in a limited area. For diffuse metastases in a limb, hyperthermic perfusion with antiblastic drugs can be considered, whereas radiation therapy can only be used for palliative purposes. The prognosis for advanced metastatic melanoma is poor. However, the introduction in the therapeutic field of new drugs—both the so-called "check-points inhibitors" and the targeted molecular therapies—have brought about a radical change in the management of these patients with a significant improvement in mean survival. The first anti-BRAF drug that showed a significant impact on the clinical course in patients with advanced metastatic melanoma was Vemurafenib, followed by Dabrafenib. These tumor growth inhibitor drugs were associated with a response rate of around 50% and a remarkable response-inducing rate, with a median of just over 1 month. However, a large percentage of patients undergo disease progression due to mechanisms of escape from BRAF inhibition, in most cases following MAP kinase pathway activation downstream of BRAF. In three randomized trials, the combined administration of anti-MEK and anti-BRAF compounds was in fact associated with a significant greater clinical efficacy compared to monotherapy, in terms of response rates (up to 68% for the "combo target"), progression-free survival and overall survival. Furthermore, the "combo target" also has a significantly better toxicity profile than monotherapy. Recently, antibody-based therapy has also been applied to combat melanoma. In particular, antibodies that bind to CTLA-4, a surface molecule on helper T cells, or to the PD-1